In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: September 6, 2017

KENNETH H. BARRETT *and* TAMMY BARRETT, *parents and representatives of* J.H.B., *deceased*,	*	PUBLISHED DECISION
Petitioners,	*	No. 14-137V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Diphtheria-Tetanus-Acellular Pertussis ("DTaP"), Hepatitis B ("Hep B"), Inactivated Polio ("IPV"), Haemophilus Influenzae Type B ("Hib"), Pneumococcal Conjugate ("Prevnar"), and Rotavirus Vaccines; Pneumonia; Death.
Respondent.	*	

Peter J. Sarda, Creech Law Firm, Raleigh, NC, for petitioners.
Robert P. Coleman, III, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On February 18, 2014, Kenneth H. Barrett and Tammy Barrett ("petitioners") filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program"),[2] on behalf of their deceased infant son, J.H.B. Petitioners alleged that as a result of receiving numerous childhood vaccines on August 28, 2013, J.H.B. died from pneumonia on August 31, 2013. Petition at ¶¶ 12-14; Amended Petition at ¶¶ 12-14. After a review of the entire record, I find that

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), **because this decision contains a reasoned explanation for the action in this case, I intend to post it on the website of the United States Court of Federal Claims.** The court's website is at http://www.uscfc.uscourts.gov. Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days of the date this decision is filed, the decision will be posted on the court's website without any changes.**

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

petitioners have provided preponderant evidence that the vaccinations J.H.B. received on August 28, 2013, caused or substantially contributed to his death. Accordingly, petitioners are entitled to compensation.[3]

I. BACKGROUND

A. Procedural History

On February 18, 2014, petitioners filed a claim alleging that as a result of receiving multiple childhood vaccinations on August 28, 2013, their minor son J.H.B. developed pneumonia and died on August 31, 2013. Petition (ECF No. 1) at ¶¶ 12-14, 17. On May 6, 2014, respondent filed his Rule 4(c) Report advising against compensation. Respondent's Report (ECF No. 9). Petitioners filed an amended petition on May 8, 2014. Amended Petition (ECF No. 11) at ¶¶ 3, 5. Neither the petition nor the amended petition stated which vaccines J.H.B. received on August 28, 2013, or which vaccines they alleged to have caused his death. The medical records indicate that on August 28, 2013, J.H.B. received Diphtheria-Tetanus-acellular-Pertussis ("DTaP"), Hepatitis B ("Hep B"), Inactivated Polio ("IPV"), Haemophilus Influenza Type B ("Hib"), Pneumococcal Conjugate ("Prevnar"), and Rotavirus vaccinations. Exhibit 4 at 2.

Petitioners filed three reports from Dr. M. Eric Gershwin, whom I accepted as an expert in rheumatology, clinical immunology, and pediatrics. Exhibit 9 (ECF No.16); Exhibit 10 (ECF No. 24); Exhibit 12 (ECF No. 28). Respondent filed two reports from Dr. Hamid Bassiri, whom I recognized as an expert in pediatric infectious diseases. Exhibit A (ECF No. 17); Exhibit C (ECF No. 26).

An entitlement hearing was held on February 8, 2016, in Washington, D.C. Petitioner Tammy Barrett (J.H.B.'s mother) and Dr. Gershwin testified on behalf of petitioners, and Dr. Bassiri testified on behalf of respondent. Transcript (ECF No. 51). Petitioners filed their post-hearing brief on May 16, 2016. (ECF No. 53). Respondent filed his post-hearing brief on June 17, 2016. (ECF No. 54). This matter is now ripe for adjudication.

B. Summary of Relevant Facts

J.H.B. was born prematurely by caesarean section on June 17, 2013, at 33 weeks and 2 days gestation. Exhibit 2 at 2. J.H.B. was admitted to the NICU immediately after birth due to prematurity and respiratory distress. *Id.* He stayed in the NICU for three weeks, and his respiratory issues were resolved on June 29, 2013. *Id.* He received his first Hepatitis B vaccination on July 8, 2013, was discharged on July 9, 2013, and did not return to the hospital for respiratory issues. *Id.* at 8-9; Tr. 107-08. J.H.B. was seen by his pediatrician at Haywood Pediatrics on July 11, 2013, July 15, 2013, and July 25, 2013. Exhibit 3 at 1. At each visit, J.H.B.'s chest and lung exams were normal and there were no respiratory concerns. *Id.* at 5-10.

[3] Pursuant to Section 300aa–13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This decision discusses the elements of the record I found most relevant to the outcome.

J.H.B. was seen for another well-child visit when he was ten weeks old, on August 28, 2013. *Id.* at 2-4. The physical examination was normal with the exception of a bump on his left wrist. *Id.* at 2. Vitals were recorded as: "Temp.: 97.9º F, Pulse: 142 (regular), Resp.: 42 (unlabored)." *Id.* The chest and lung exam revealed "normal excursion with symmetric chest walls, quiet, even and easy respiratory effort with no use of accessory muscles and on auscultation, normal breath sounds, no adventitious sounds and normal vocal resonance." *Id.* at 3; *see also* Tr. 109 (mother's testimony that on August 28, 2013, J.H.B. had "no sniffling, no sneezing, no coughing, no nothing"). On August 28, 2013, at approximately 3:20 p.m., J.H.B. received DTaP, Hep B, IPV, Hib, Prevnar, and Rotavirus vaccinations. Exhibit at 3-4; Exhibit 4 at 2.

J.H.B.'s mother testified that after receiving the vaccinations, J.H.B. was cranky and cried more than usual. Tr. 110-12. The next day, August 29, 2013, he was sleepy but did not have a fever. *Id.* at 112-13. He did not develop a fever at any time in the subsequent days. On August 30, 2013, J.H.B.'s mother fed him and put him to bed shortly thereafter, around 11:00 p.m. *Id.* at 113. The next day, August 31, 2013, at approximately 5:30 a.m., the mother awoke and found J.H.B. cold to the touch. *Id.* at 111; Exhibit 7 at 3. Haywood County EMS was dispatched to J.H.B.'s home due to a report of "cardiac arrest." Exhibit 5 at 1-2. EMS arrived at 6:04 a.m. and found J.H.B. pulseless and breathless. *Id.* at 2. J.H.B. was pronounced dead at 6:16 a.m., August 31, 2013. *Id.*[4]

An autopsy was performed on September 2, 2013. Exhibit 7 at 3. The autopsy report includes a summary of an interview with J.H.B.'s mother, in which she stated that after J.H.B. received the vaccinations on August 28, 2013, J.H.B. "appeared to sleep more and was only active when feeding." *Id.* at 3. J.H.B.'s mother further stated that J.H.B. was last seen alive at approximately 11:00 p.m. on August 30, 2013, when he was fed and put to bed. *Id.* "At some point the mother discovered the infant non-responsive and cold to the touch." *Id.* Cultures of the left lower lung were positive for Escherichia coli, Klebsiella pneumoniae, and Enterococcus faecalis. *Id.* at 4. However, these were thought to be contaminant. *Id.* A nasopharyngeal swab was positive for rhino/entero virus. According to the autopsy report's microscopic description, "the lungs demonstrate[d] atelectasis and widespread widening of the alveolar septa with increased chronic

[4] By my calculation, approximately 56 hours passed between the approximate date and time of vaccination (August 28, 2013 at 3:20 p.m.) and when J.H.B. was put to bed and was last observed alive (August 28, 2013, at 11:00 p m.). Approximately 63 hours passed between the vaccinations and the pronouncement of death (August 31, 2013, at 6:16 a.m.).

inflammatory cells[5] more significant in the right lung." *Id.* at 7. The medical examiner concluded that the cause of death was "[a]cute viral pneumonia."[6] Exhibit 5 at 5.

C. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. Section 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

To receive compensation under the Program, a petitioner must prove either a "Table" injury[7] or a causation-in-fact injury, i.e. that a vaccine listed in the Table was the cause in fact of an injury (an "off-Table" injury). *See* Sections 300aa-13(a)(1)(A) and 11(c)(1); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). While the Table includes many of the vaccines received by J.H.B., it does not list those vaccines in relation to fatal pneumonia within the timeframe present in this case. Thus, petitioners allege that J.H.B. suffered an "off-Table" injury.

To establish entitlement to an "off-Table" injury, a petitioner must demonstrate by a preponderance of the evidence: (1) that he received a vaccine or vaccines set forth on the Vaccine Injury Table; (2) he received the vaccine(s) in the United States; (3) he sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) his condition has persisted for more than six months or resulted in death. Section 13(a)(1)(A). To satisfy the burden of proving causation-in-fact, a petitioner must establish each of the three *Althen* factors by preponderant evidence: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that

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[5] As discussed below, petitioners' expert Dr. Gershwin and respondent's expert Dr. Bassiri both considered the finding of chronic inflammatory cells to be significant to their opinions. Dr. Gershwin stated that inflammation could be attributable to either one of two distinct innate immune responses: a Th-1 response (which is most effective against infection) or a Th-2 response (which is designed to respond to bacteria, and according to Dr. Gershwin, the alum contained in vaccines). Dr. Gershwin opined that if these chronic inflammatory cells had been isolated and analyzed, they would reveal a Th-2 response (to the alum in the vaccines). Dr. Bassiri disagreed. He believed, based on the age of the cells, that they would have shown a Th-1 response (to an infection predating the vaccinations). Based on the experts' extended discussion of these cells, at the end of the entitlement hearing, I directed petitioners' counsel to inquire as to whether any samples of the cells were available for analysis. On February 16, 2016, petitioners' counsel filed a status report indicating that the pathology department at Wake Forest Medical Center had indicated that no "wet tissue samples" were available for analysis. ECF No. 48. The pathology department did send some photographs of J.H.B.'s lungs. *Id.* Neither expert rendered any additional opinion based on the photographs.

[6] Pneumonia is defined as inflammation of the lungs with consolidation. Acute pneumonia is "severe" and "of rapid onset." Viral means "caused by a virus." Dorland's Illustrated Medical Dictionary (32d ed. 2012) (hereinafter "Dorland's") at 1472-74.

[7] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2017), corresponding to the vaccine received within the timeframe specified.

each *Althen* factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. *See Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991).

With regard to the first prong, in *Althen*, the Federal Circuit noted that "while [the petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (emphasis added).

Under the second *Althen* prong, petitioners need to show that the vaccines at issue were "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999). Petitioners do not need to show that the vaccines were the "sole" or even the "predominant" cause. *Id.* at 1352. For example, in *Shyface*, the Federal Circuit affirmed the special master's finding that the petitioners were entitled to compensation, based on their expert's testimony that the vaccine together with a bacterial infection caused the child's high fever and death (although the expert could not testify that the vaccine was the "sole" or "predominant" cause). *Id.* at 1353.

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate "[t]he factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280.

In determining whether petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Services*, 569 F.3d 1367, 1380 (Fed. Cir. 2009) (referencing *Althen*, 418 F.3d 1274; *Capizzano*, 440 F.3d 1317).

II. EXPERT OPINIONS

A. Petitioners' Expert Dr. M. Eric Gershwin

Dr. Gershwin received his medical degree from Stanford University in 1971. Tr. 11; Exhibit 9-A at 1. He did an internship and residency at the Tufts-New England Medical Center in Boston and then trained in clinical immunology at the National Institutes of Health. Exhibit 9-A at 3. In 1982, Dr. Gershwin was hired by the University of California – Davis School of Medicine to develop a program in immunology. *Id.*; Tr. 11. He is presently the Distinguished Professor of Medicine and the chief of the division of rheumatology/allergy and clinical immunology at UC Davis. Tr. 12. This role involves patient care, teaching, research, and supervising faculty. *Id.* He is board-certified in internal medicine, rheumatology, and allergy immunology with a conjoined board in pediatric allergy immunology. *Id.* At the entitlement hearing, petitioners' counsel asked Dr. Gershwin to explain his "role in developmental immunology." *Id.* at 13. Dr. Gershwin responded: "Developmental immunology is an understanding of how the immune system develops over time, in the embryo, during the newborn period. It's also a comparative field, which relates not only to humans, but to animals." *Id.* at 13-14. I accepted Dr. Gershwin as an expert in the fields of rheumatology, clinical immunology, and pediatrics. *Id.* at 15.

i. Medical Theory

Dr. Gershwin's theory was that the alum used as an adjuvant in certain vaccines can temporarily skew a premature infant toward a Th-2 innate immune response, allowing a common viral infection to become fatal.

Dr. Gershwin explained that an infant, particularly one born prematurely, has not developed an adaptive immune system and is therefore heavily dependent on his innate immune system. Exhibit 9 at 1; Tr. 16. Furthermore, the infant's innate immune system is qualitatively and quantitatively different than that of an adult. Exhibit 9 at 1[8]. The infant's innate immune system is biased toward a Th-2 type response which involves the release of cytokines including IL-4. Tr. 16-19. This response is effective at fighting bacteria. Tr. 19. The infant is biased against a Th-1 response, which produces cytokines such as gamma interferon that are very cytotoxic[9] and more effective at fighting viral infections. Tr. 16-19.[10] Dr. Gershwin opined that an infant's reliance on the innate immune system and the tendency toward a Th-2 response makes the infant more

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[8] Citing Exhibit 9, Tab C2, Peter Ghazal et al., *Early Life Response to Infection*, 26 CURR. OPIN. INFECT. DIS. 213, 214 (reporting that infants have comparatively lower levels of IL-12, type I IFNs and IFNy, but higher levels of IL-1β, IL-6, IL-23 and IL-10; also suggesting the presence of a "strong but highly regulated negative feedback response… between components of the innate arm"); *see also* Exhibit 9, Tab C1, Sudhin Thayyil-Sudhan et al., *Safety and Effectiveness of BCG Vaccination in Preterm Babies*, 81 ARCH. DIS. CHILD FETAL NEONATAL 64 (1999).

[9] Cytotoxicity is defined as "the degree to which an agent possesses specific destructive action on certain cells or the possession of such action; used particularly in referring to the lysis of cells by immune phenomena." Dorland's at 467.

[10] Dr. Gershwin agreed that either a Th-1 or Th-2 response would produce "visible inflammation." Tr. 21-25. The observation of inflammation is non-specific; it indicates only that some kind of immune response has occurred. Tr. 21. A pathologist would need to isolate the white blood cells and stimulate them in vitro to determine whether they produce Th-1 or Th-2 cytokines. Tr. 21.

"susceptible" to viral infection. Exhibit 9 at 1. However, the infant should still manage to fight off infection. *Id.* at 2.

Dr. Gershwin opined that alum, which is used as an adjuvant[11] in certain vaccines, will also skew the immune system toward a Th-2 response.[12] Dr. Gershwin generally supports the use of alum as an adjuvant in vaccines. Tr. 16-17. He stated that in most cases, alum does not have a harmful effect. If an infant does not have an infection, the alum "won't make any difference." Tr. 20. If an infant is not born prematurely and is older, "it may not make a difference." Tr. 20. However, prematurity, young infancy, and alum *all together* can skew an infant's immune response so far toward a Th-2 response that it cannot defend against a viral infection. Tr. 17, 20. Dr. Gershwin used the metaphor of a seesaw. One or two factors may not tip the seesaw. However, all three factors together make the seesaw "ti[p] against" the infant with a viral infection. Tr. 20.[13]

Dr. Gershwin acknowledged: "Th-2 skewing has not been clearly demonstrated in human viral infections." Exhibit 10 at 2.[14] He provided two articles linking alum to "cytokine switches and specific immune responses" in mice. Exhibit 10 at 4. In the first article, McKee et al.[15] state that "alum usually generates Th-2 related specific immune responses, [in part by] induc[ing] production of IL-4[, which] acts by suppressing Th-1 related phenomena, leading to a more polarized immune response." Exhibit 42 at 4. McKee et al. then report the results of injecting alum into the peritoneum or hind calf muscles of mice: "[w]ithin hours of exposure, alum induces a type 2]Th-2] innate response characterized by an influx of eosinophils, monocytes, neutrophils, DC, NK

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[11] Alum "combin[ed] with soluble antigen forms a precipitate; slow release of the antigen from the precipitate on injection causes prolonged, strong antibody response." Dorland's at 32.

[12] Dr. Gershwin stated that Hib, Pneumococcal, and DTap childhood vaccines contain alum. Exhibit 9 at 3; Tr. 16.

[13] Dr. Gershwin also suggested contributions from a "cardiorespiratory event." Citing Exhibit 14, Pourcyrous et al., *Primary Immunization of Premature Infants with Gestational Age < 35 Weeks: Cardiorespiratory Complications and C-Reactive Protein Responses Associated With Administration of Single and Multiple Separate Vaccines Simultaneously*, 151 JOURNAL OF PEDIATRICS 167 (2007). This article largely seems to relate to *Althen* prong three, and is discussed at further length in those sections of the opinion. But relevant to *Althen* prong one, Pourcyrous observed that 16% (39/ 239) of preterm infants who received vaccinations subsequently experienced "cardiorespiratory events," namely, new or increased apnea, bradycardia, or O2 desaturation. Exhibit 14 at 2. These events improved or resolved within 72 hours of onset. Exhibit 14 at 2. Dr. Gershwin testified that multiple vaccinations are associated with "cardiorespiratory complications [but they] *won't be clinically significant unless you also have an infection going on*." Tr. 31 (emphasis added). Pourcyrous did not study infections. Therefore, this is Dr. Gershwin's own opinion.

[14] Quoting Exhibit 17, Andrew T. Borchers, Christopher Chang, M. Eric Gershwin & Laurel J. Gershwin, *Respiratory Syncytial Virus—A Comprehensive Review*, 45 CLINIC. REV. ALLERG. IMMUNOL. 331, 347 (2013). This article notes that there is "limited information on the normal human immune response" to primary respiratory syncytial virus ("RSV") because (1) it is normally mild and lab tests are only ordered in the most severe cases and (2) it "occurs at such a young age that sampling is usually limited to the nasal lavage or nasopharyngeal aspirates (NPA) routinely taken for diagnostic and therapeutic purposes and non-bronchoscopic BAL fluid obtained from mechanically ventilated patients." Exhibit 17 at 341. "Therefore, much of the information currently available on the human immune response to RSV infection comes from experimental models." Because it is difficult to collect data on the human immune response to RSV (and other viral infections), many studies are on mice. Exhibit 17 at 342.

[15] Exhibit 42, Amy S. McKee et al., *Alum Induces Innate Immune Responses Through Macrophage and Mast Cell Sensors, But These are Not Required for Alum to Act as an Adjuvant for Specific Immunity*, 183 J. IMMUNOL. 4403 (2009).

cells, and NKT cells. In addition, at least thirteen cytokines and chemokines are produced within 4 hours of injection including IL-1β and IL-5." Exhibit 42 at 3 (quoted in Dr. Gershwin's first report, Exhibit 9 at 3).

In his first report, Dr. Gershwin does not discuss how McKee et al. or other studies on mice apply to his theory about infants. Exhibit 9 at 3. In his second report, he states: "The quantitative issue of alum in mice is not relevant. The effect of alum is not necessarily dose dependent and indeed the doses that are generally given in mice are higher than given in humans. The plausibility remains the same." Exhibit 10 at 4. In his third report, he writes: "Alum does have the potential to skew the immune response. Indeed, as referenced in my other reports, it has been specifically used to skew a response." Exhibit 12 at 2.

At the entitlement hearing, Dr. Gershwin introduced an article by Kim et al.[16] and related both mouse studies to his theory about how alum contained in vaccines may affect human infants. Kim et al. immunized mice intranasally with FI-RSV[17] "with or without alum (20 μg[18] or 5 μg in 100 μl FI RSV per mouse)." Exhibit 44 at 3. They reported that alum was associated with "higher levels of RSV F-specific antibody secreting cell spots in spleen and bone marrow samples." Exhibit 44 at 8. Alum was also associated with "inflammation, mucus production, and eosinophilia" in the lung tissues. Exhibit 44 at 10; *see also* Tr. 38 (Dr. Gershwin: "on page 10, they say the same thing I have, that alum induces Th-2 and cytokine responses"). Alum was associated with higher levels of IL-4 and IL-6 in the lung tissue. Exhibit 44 at 12, Figure 7; *see also* Tr. 38 (Dr. Gershwin: Figure 7 shows "these same cytokines are found in the lung"). Alum was also found to inhibit IFN-y CD8 T cell responses. Exhibit 44 at 14, Figure 8; *see also* Tr. 38 (Dr. Gershwin: Figure 8 shows that the cytokines "inhibit some immune function"). Kim et al. conclude: "these results in this study are consistent with previous studies reporting that Th-2 cytokines and chemokines were associated with pulmonary eosinophilia and RSV vaccine-enhanced disease." Exhibit 44 at 16.

Dr. Gershwin stated that the McKee and Kim studies show that alum is "potentially harmful" to mice. Tr. 34-41, 96. He stated that vaccines can deliver "comparable" doses of alum to infants. Tr. 37-38. He also stated that only a certain amount of alum can adsorb to an antigen. Tr. 35-37. Any excess alum is "washed away." Therefore, the mice may have received alum in excess of the doses necessary to have a negative effect. Dr. Gershwin also faulted Dr. Bassiri's assumptions about McKee et al. That study administered "2-5 mg of Alhydrogel or, in some experiments, alum precipitated in our laboratory." Exhibit 42 at 3. Dr. Gershwin stated that Dr. Bassiri assumed that each mouse received 2-5 mg of precipitated alum, which would be

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[16] Exhibit 44, Ki-Hye Kim et al., *Alum Adjuvant Enhances Protection Against Respiratory Syncytial Virus but Exacerbates Pulmonary Inflammation by Modulating Multiple Innate and Adaptive Immune Cells*, 10 PLOS ONE 1 (2015). Dr. Gershwin's and respondent's expert Dr. Bassiri's expert reports were submitted in 2014 - 2015. This article by Kim et al. was published in late 2015. Petitioners filed the article on February 3, 2016. At the beginning of the entitlement hearing on February 7, 2016, the parties and I agreed that this article could be considered as part of the record. Tr. 5-9. Therefore, this article was discussed by the experts only during the entitlement hearing. The parties also referred to the article in their post-hearing briefs.

[17] RSV is a common medical abbreviation for respiratory syncytial virus. Davis, *Medical Abbreviations* (15th Ed.) at 286.

[18] Dr. Gershwin noted that McKee administered alum in doses of micrograms ("μg"). As discussed below, Kim administered doses of milligrams ("mg"). "One milligram would be a thousand times higher than a microgram." Tr. 37.

significantly different than 2-5 mg of Alhydrogel, which is only 2% alum. Tr. 37-40. Dr. Gershwin also critiqued Dr. Bassiri's ratio of dose to recipient's body weight. Dr. Gershwin stated that it was also important to consider the recipient's body surface area when evaluating the impact of alum. Tr. 37-40. In summary, Dr. Gershwin contended that McKee and Kim show that alum can create a "skewing" toward a Th-2 response in mice and may indeed have that effect on human infants.

As will be discussed below, respondent's expert Dr. Bassiri asserted that prior to being vaccinated, J.H.B. had pneumonia, which would terminally differentiate cells to a Th-1 phenotype and those differentiated cells could not later be "unskewed" or "reskewed" to a Th-2 phenotype. In response, petitioners' expert Dr. Gershwin stated that if J.H.B. did have a pneumonia that was kept at bay by an effective Th-1 immune response, consistent with having no fever, then it is unlikely that he would have died. Tr. 28-29. Dr. Gershwin did not claim that introducing alum would "unskew" cells that had differentiated to the Th-1 phenotype. He just responded that introducing alum would direct new, undifferentiated cells toward the Th-2 phenotype and away from the Th-1 phenotype. Thus, in the short window of time during which J.H.B. needed to fend off the ongoing mild viral infection, J.H.B.'s Th-1 response was insufficient, resulting in his death. Tr. 27-29.

Dr. Gershwin disagreed with Dr. Bassiri's assertion, discussed below, that there would be a spike in mortality during cold season if vaccines were really skewing the immune response to the extent Dr. Gershwin suggests, because physicians would not immunize a child who has signs of pneumonia. Tr. 95. In his second and third reports, Dr. Gershwin also emphasized the importance of "individual genetic factors [that] play a role in susceptibility to disease and in response to antigenic stimulation, whether by vaccines or infections." Exhibit 10 at 1; Exhibit 12 at 1.

Dr. Gershwin also noted that it would be very rare for a young infant born prematurely to contract an infection and then be vaccinated. Medical professionals generally do not vaccinate visibly sick children. Therefore, he suggested, epidemiology may not be able to detect such rare events.

Dr. Gershwin stated that infants often contract common viral infections such as rhinovirus or enterovirus, which "ought to be innocuous." Tr. 18. "Most kids, the vast, vast majority, will not die of an entero or rhinoviral pneumonia unless they have some otherwise significant compromise of their immune system." Tr. 20, 27. Dr. Gershwin also stated that rhino- and enterovirus are less aggressive than RSV or influenza. Tr. 95. They are rarely fatal. However, the infant's immune system still needs to respond effectively and prevent such infections from progressing. Unfortunately in this case, by a coincidence of timing, J.H.B. was exposed to a rhino- or enterovirus at or around the time he was vaccinated, when the effects of prematurity, infancy, and the alum in his vaccinations all combined to skew his immune system toward an ill-suited Th-2 response. This skewing rendered his immune system unable to fight what would normally be an innocuous viral infection, instead resulting in his death. Dr. Gershwin made clear that the alum in the vaccines was one of many "little blocks that [added] up," and had a cumulative effect. Tr. 26.

ii. Logical Sequence of Cause and Effect

Dr. Gershwin opined that there was a logical sequence of cause and effect in which the alum in multiple vaccines skewed J.H.B. further away from a Th-1 response, allowing a previously asymptomatic, mild infection to develop into fatal pneumonia. Dr. Gershwin stated that at baseline, J.H.B.'s immune system was not as robust as that of a full-term infant. J.H.B. was already biased

toward a Th-2 response. Therefore, J.H.B. was at "increased risk of infection." Exhibit 9 at 3; *see also* Exhibit 10 at 4; Tr. 25-26.

Dr. Gershwin stated that "the best of all answers based on the data… and the epidemiology of rhino or enterovirus is that it probably was already in his carriage." Tr. 41. Dr. Gershwin opined that J.H.B. had the viral infection before going to the doctor or perhaps he picked it up in the doctor's office. Tr. 41. It was "minor but not clinically significant." Tr. 18. J.H.B. appeared healthy, his appetite was reported to be normal, he was not fussy, and he did not have a fever. Exhibit 9 at 2. His respiratory rate was normal, his chest seemed clear, and his breath was not labored. Tr. 95.

Dr. Gershwin opined that if J.H.B. had the infection prior to vaccination, he was still able to keep it "at bay" and "control it" until he received the vaccinations. Tr. 29, 41. J.H.B. then received vaccinations that collectively contained an amount of alum "certainly comparable to the amount of alum which has been shown to be potentially harmful in [the McKee et al. and Kim et al.] mouse studies." Tr. 37-40.[19] This alum temporarily skewed J.H.B. toward a Th-2 response and away from the Th-1 response that had begun against the infection. Exhibit 9 at 3; Exhibit 10 at 4; Tr. 16-17, 27-28. Within 63 hours of the vaccinations, the infection progressed and led to death. Dr. Gershwin believed that if not for the alum in the vaccines, more likely than not, J.H.B. would not have had a fatal outcome. Exhibit 9 at 4; Exhibit 10 at 4; Tr. 28.

Dr. Gershwin disagreed with Dr. Bassiri's contention (discussed below) that the preexisting infection would have activated J.H.B.'s immune system to a Th-1 response which would have continued even after the alum was introduced. Dr. Gershwin stated that if this normal Th-1 response had continued, J.H.B. "shouldn't have died." Tr. 28-29.

Dr. Gershwin insisted that there was no alternative explanation for J.H.B.'s death. Exhibit 12 at 3. He did not see any evidence that J.H.B. suffered from a primary immune deficiency disease. Tr. 43. He also said that prematurity and infancy made J.H.B.'s immune system "less robust" but not totally compromised. Exhibit 9 at 3. Therefore, only the prematurity, infancy, and alum all together "tipped" J.H.B. to a fatal outcome.

Dr. Gershwin noted that the autopsy report mentioned "increased chronic inflammatory cells" in the lungs. Exhibit 7 at 7. He stated that this was made up of "infiltrating *mononuclear* cells." Tr. 21. He stated that the word "'chronic' implies that the cells were mononuclear, which is what you'd expect of a virus." Tr. 26. Dr. Gershwin opined that *if* the cells had been isolated, they would have reflected a skewed Th-2 response. Tr. 21. However, "we have no evidence of any skewing… nothing was done to even attempt to do that." Tr. 28. Dr. Gershwin also noted that the

[19] Dr. Bassiri calculated and Dr. Gershwin agreed that J.H.B.'s vaccinations contained approximately 1.2 mg of alum. Exhibit A at 4; Tr. 35.

autopsy report did not include "any significant immunophenotyping"[20] or "definition of memory[21] versus effector cells."[22] Exhibit 12 at 2.

Dr. Gershwin also disagreed with Dr. Bassiri's contention (below) that the chronic inflammatory cells would have taken at least 3-5 days to influx, which would indicate they were present before the vaccinations. Dr. Gershwin critiqued Dr. Bassiri for relying on animal studies for this point. Dr. Gershwin opined that animal studies would not predict what would happen in an infant: "the kinetics would be different." Tr. 93-94. Dr. Gershwin acknowledged that he could not "put a clock" on how long those cells would take to develop. Tr. 27.

iii. Timing

As discussed above, Dr. Gershwin's theory was that vaccines containing alum would temporarily skew a premature infant toward a Th-2 response and away from a Th-1 response, allowing an incipient viral infection to progress and become fatal. He stated that the skewing would occur "in the short term," during an "unfortunate window of opportunity for the host." Tr. 18.

Dr. Gershwin also testified that the immune system can produce inflammation "within hours." Tr. 22. An innate immune response "occurs very, very quickly." Tr. 30, 98. He stated the innate immune response can be observed when "you get a splinter, your finger is swollen and there are mononuclear cells there." Tr. 30, 98. Dr. Gershwin stated that similarly alum would skew the innate immune response "within hours." Tr. 30.

Dr. Gershwin provided three articles relating to timing. First, McKee et al. observed that mice displayed a Th-2 innate response (specifically, the production of cytokines) within 4 hours of exposure to alum. Exhibit 9 at 3 (citing Exhibit 42 at 3). Second, I asked Dr. Gershwin about Kim et al.'s findings of "severe pulmonary inflammation… correlat[ing] with high levels of infiltrating immune cells and granulocytes, particularly eosinophils, mucus, and eotaxin production as well as IL-6 and IL-4 inflammatory cytokines in the lung and BAL fluids" of mice. Tr. 98 (quoting Exhibit 44 at 16). These various samples were taken 3-5 days after the mice were exposed to RSV with alum. Exhibit 44 at 3. Dr. Gershwin stated that this innate response would "occur more quickly than the three to five day time period." Tr. 98.

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[20] Immunophenotyping is "analysis of the antigens expressed by cells." Dorland's at 920.

[21] Memory cells are "T and B cell lymphocytes… believed to retain memory" about their first exposure to an antigen, in order to effectuate a "more rapid, efficient immune response on subsequent exposures." Dorland's at 320. Therefore, they are part of the adaptive immune system.

[22] Effector cells are "differentiated lymphocyte[s] that carr[y] out some part of the immune response. e.g., antibody production, lymphokine production, or helper, suppressor, or killer function." They are not said to have any "memory." Dorland's at 316.

Third, Dr. Gershwin provided an article by Pourcyrous et al.[23] This was an observational study of 239 preterm infants under two months of age. Seventy percent of the infants given a single vaccine and 85% of the infants given multiple vaccines[24] had abnormal elevation of C-reactive protein ("CRP") within 3 days (72 hours). Exhibit 14 at 2-3. Pourcyrous stated that CRP might be associated with "swelling and redness at the immunization site or fever… [or] immune activation." Exhibit 14 at 4. Pourcyrous also stated that the variation in magnitude in CRP response to immunization may be attributed to the type of antigen, quantity of antigens in a given vaccine, number of vaccines, presence and quantity of alum adjuvant, genetic polymorphism, and decreased immunologic responses in some preterm infants. Exhibit 14 at 2.

Pourcyrous also reported that 16% (39/239) of the infants had "immunization-associated cardiorespiratory events," namely, new or increased apnea, bradycardia, or oxygen desaturation. Exhibit 14 at 2. The onset of symptoms ranged from "4 to 66 hours (mean ±SD of 25 ± 15 hours, median of 21 hours)" after vaccination. Exhibit 14 at 2. "Ninety-five percent (37/ 39) of cardiorespiratory events occurred within 48 hours post-immunization." Exhibit 14 at 2. Based on this study and others, Pourcyrous recommended that preterm infants receiving vaccinations be "closely monitored for up to 48 hours… because of the risk of cardiorespiratory events." Exhibit 14 at 4.

Dr. Gershwin stated that Pourcyrous was "consistent with" his opinion about the timing and "highlighted this point about the inflammation that I've talked about." Tr. 30-31. Dr. Gershwin claimed that Pourcyrous offered the "identical plausible explanation that I've offered, which is the multiple vaccines, the presence of alum, the genetic differences, [and] the decreased immunological responses in some pre-term infants" have a harmful effect. Tr. 97.

Dr. Gershwin's opinion was that alum would have the short-term effect of skewing the immune system toward a Th-2 response, during a narrow window of opportunity when the immune system instead needed to respond to a mild virus. Dr. Gershwin considered the timing of this case. In his first report, Dr. Gershwin stated that J.H.B. received the vaccinations on August 28, 2013; afterward, in the afternoon, J.H.B. was crying and appeared distressed, which continued until the evening of August 29, 2013; on August 30, 2013, J.H.B. appeared sleepy; and in the early morning of August 31, 2013, he was found unresponsive and pronounced deceased. Exhibit 9 at 1. This initial summary from Dr. Gershwin accurately reflects that less than 72 hours passed between J.H.B.'s vaccinations and his death.[25] At trial, Dr. Gershwin also stated that "everything came… in that 48-to-72-hour window." Tr. 27.[26] He testified that alum preferentially helps us develop long-term immunity. Tr. 18. However, alum can temporarily skew a susceptible host's immune

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[23] Exhibit 14, Pourcyrous et al.

[24] Namely, DTaP, Hib, PCV7, IPV, and/ or HBV. Exhibit 14 at 2.

[25] *See also* Summary of Relevant Facts (finding that J.H.B. was vaccinated on August 28, 2013, at approximately 3:20 p m. and was pronounced dead on August 31, 2013, at 6:16 a.m.); footnote 5 (calculating a timeframe of 63 hours between these events).

[26] *But see* Tr. 30 (when asked directly whether the timeframe was medically acceptable, Dr. Gershwin stated that he "forgot the hours" and he gave a much shorter time period of "16, 17 hours" between J.H.B.'s vaccinations and death).

response toward Th-2. In this case, the temporary skewing created an unfortunate window of opportunity for the viral infection to develop and become fatal for J.H.B.

B. Respondent's Expert, Dr. Hamid Bassiri

Dr. Bassiri received a Ph.D. in immunology from the University of Pennsylvania in 2002 and his medical degree from the same institution in 2004. Exhibit B at 1. He did a residency in general pediatrics at the Children's Hospital of Philadelphia from 2004 to 2007, followed by a fellowship in pediatric infectious diseases from 2007 to 2010. *Id.*; Tr. 46. He is currently employed as a clinical attending physician for pediatric infectious diseases at the Children's Hospital of Philadelphia and as assistant professor of pediatrics at the University of Pennsylvania School of Medicine. Tr. 45. He is board-certified in general pediatrics and pediatric infectious diseases and specializes in the care of the immunocompromised host. *Id.* at 46. I admitted Dr. Bassiri as an expert in pediatric infectious diseases. *Id.* at 50.

i. Response to Petitioners' Theory

Dr. Bassiri agreed that compared to older children and adults, infants demonstrate "qualitatively and quantitatively different" immune responses which make them "susceptible to infectious diseases." Exhibit A at 4. "Premature infants (and especially very premature infants born less than 29 weeks of gestation) may be at highest risk." *Id.* Dr. Bassiri also agreed that infants are predisposed to a Th-2 response. Exhibit A at 4. However, he contended that both premature and full-term infants have been "documented to be similarly capable of mounting cell-mediated immune responses." Exhibit A at 4; Tr. 56. His reference for this proposition was a study by Thayyil-Sudhan et al., filed by petitioners. Exhibit A at 4.[27] Dr. Bassiri stated that Thayyil-Sudhan found that "*pre-term* (with a mean age of 33 weeks – same as J.H.B.) *and full-term neonates* immunized with BCG showed similar Th-1 responses… This study indicates that despite the apparent predisposition toward Th-2 type immunity, Th-1 cell-mediated responses are still elicited and are not overwhelmingly impaired, even in premature human neonates." Exhibit A at 4 (emphasis added); *see also* Tr. 61.

Dr. Bassiri agreed with Dr. Gershwin "that the administration of alum also predisposes to a Th-2 type response." Tr. 56. Dr. Bassiri then disputed that the amount of alum in the multiple vaccines given to a child would be sufficient to have that effect. Dr. Bassiri stated that the use of alum as an adjuvant "allows for adsorption of protein antigen to its particulate crystalline structure . . . thereby concentrating the antigen and permitting its slow release." Exhibit C at 1. He stated that the dose of alum is relevant and the effects of alum are dose-dependent. *Id.* at 2. Although small doses of alum may adequately adsorb the vaccine antigens, this may not result in an optimally adjuvanted response. *Id.*

Because Dr. Bassiri thought the dose of alum is relevant and the effects of alum are dose-dependent, he paid close attention to the doses given in the McKee and Kim studies and he evaluated whether those studies were applicable to human infants receiving vaccines. He stated that the McKee study was inapplicable, first, because "the majority of the data is from… the site of alum administration, i.e., the mice's peritoneal cavity." Exhibit A at 4. Dr. Bassiri opined that McKee

[27] Citing Exhibit 9, Tab C1, Sudhin Thayyil-Sudhan et al.

shows that alum can have a local effect, but it does not dramatically alter the entire immune response "such that the *entire* T cell repertoire would be skewed away from a Th-1 phenotype." Exhibit A at 4; Tr. 65-66.

Dr. Bassiri's second argument was that McKee's results were from administering a very large dose of alum relative to a mouse's body weight. Exhibit A at 4. Dr. Bassiri assumed that McKee gave each mouse 2-5 mg of precipitated alum. *Id.* Dr. Bassiri calculated that 2-5 mg of precipitated alum relative to a mouse's body weight, was 1,000 times greater than the alum given to an infant relative to an infant's body weight. Exhibit A at 4. Based on this calculation, Dr. Bassiri opined, it is "entirely speculative that the small effective dose of alum [administered to an infant] could exert such a profound and systemic effect – to the point that the cell-mediated immune response would be unable to control a viral infection." Exhibit A at 4. Dr. Bassiri later acknowledged that in certain experiments, McKee used Alhydrogel, which is only 2% alum. Tr. 63. Thus, when the Alhydrogel solution was administered, the dose of alum relative to the mouse's body weight was only 40 times greater than the dose of alum in vaccines relative to an infant's body weight. Tr. 63. Dr. Bassiri stated that this difference "would still be relevant" to his argument. Tr. 63.

Dr. Bassiri contended that the study by Kim et al. also supported his contention that alum has dose-dependent effects. Kim found that a mouse receiving 5 μg of alum "displayed less weight loss and suppressed mucus production as well as cleared lung viral loads" compared to a mouse receiving 20 μg of alum. However, even the 5 μg dose resulted in significant reductions of IL4 producing Th-2 cells.

He also claimed that if *any* alum affects immune responses, it would be the alum that is ingested regularly. Exhibit A at 5. He stated that each day, an infant such as J.H.B. ingests 1 liter of formula containing approximately 0.225 mg of aluminum. *Id.* "As such, it would appear that [a child] would be exposed to substantially more aluminum prior to ever receiving his 2-month vaccines. Thus, if it is to be believed that aluminum does skew the immune response, it would be more apt to be caused by the ingestion of aluminum and its constant levels in the blood, rather than the small additional doses administered via vaccination." *Id.*[28]

Dr. Bassiri argued that even in a situation where alum *would* produce some skewing toward a Th-2 response, the alum would not "preclude the ability to mount a Th-1 response." Tr. 56. Dr. Bassiri's opinion was based on a fact pattern in which the first thing present is a viral infection. Tr. 56-57. In response, naïve T cells would skew toward a Th-1 phenotype. Tr. 57. Once those naïve T cell differentiate, they cannot be easily switched to another phenotype (Th-2). Tr. 57.

Dr. Bassiri acknowledged that while a viral infection is present in the body, the immune system mounts an initial response and then *continues* to respond: it "puts out millions of naïve T cells per day." Tr. 58. He believed that the initial skewing toward the Th-1 response is most important. *Id.* at 59. However, he did not know if alum was introduced, whether "new cells" would

[28] Dr. Bassiri agreed that the multiple vaccines received by J.H.B. contained about 1.2 mg of alum. Exhibit A at 4.

add to the Th-1 response or would skew toward a separate Th-2 response. Tr. 59-60. Dr. Bassiri did not have a direct answer to that question, based on the literature. Tr. 59-60.[29]

Dr. Bassiri opined that if the alum in vaccines prevented infants from mounting effective Th-1 responses, he would expect to see a spike in infant mortality after vaccines, as viruses such as rhino and enterovirus are very common. Exhibit A at 5; Tr. 60. He stated that Otto et al. found that infants vaccinated for diphtheria, pertussis, tetanus, polio, and Hib within the first 60-90 days of life were less likely to display symptoms of viral infections. Exhibit A at 5.[30] Thus, if vaccines are skewing, "they are not skewing to the point where children cannot mount an effective Th-1 response." Tr. 61. Dr. Bassiri agreed with Dr. Gershwin that a pediatrician would not vaccinate a child who appeared to be very sick. Tr. 69. However, he noted that the American Academy of Pediatrics still recommends vaccination in children who have common viral illnesses. Exhibit C at 2-3; Tr. 69. He stated that the Institute of Medicine concluded that "the existing data favored rejection of a causal connection between multiple vaccinations and susceptibility to heterologous infections." Exhibit A at 5.[31] He also contended that epidemiology would have detected a link between alum-containing vaccines and susceptibility to infections, even in children with rare "specific genetic makeups," based on the "hundreds of millions of doses [of] vaccines administered worldwide during viral seasons… Because such a signal has not been described, the empiric data show that Dr. Gershwin's hypothesis is likely incorrect." Exhibit C at 2-3.

ii. Response to Petitioners' Argument of a Logical Sequence of Cause and Effect

Dr. Bassiri agreed that based on J.H.B.'s premature birth at 33 weeks, J.H.B. was "at higher risk (although perhaps not the highest risk category) for invasive infections." Exhibit A at 4.

Like Dr. Gershwin, Dr. Bassiri believed that J.H.B. had an infection prior to vaccination. Tr. 51. Dr. Bassiri based this opinion on the autopsy finding of increased chronic inflammatory cells in J.H.B.'s lungs. Exhibit A at 3. Dr. Bassiri opined that "chronic inflammatory cells" usually mean mononuclear cells, which can be T cells, B cells, or natural killer cells.[32] Exhibit A at 6; Tr. 91, 99. Dr. Bassiri opined that it would have taken 3-5 days for mononuclear cells to influx in J.H.B.'s lungs. Tr. 83-89.[33] This process must have started before J.H.B. was vaccinated, because

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[29] Dr. Bassiri did not respond to Dr. Gershwin's citation to McKee et al., who stated that a Th-2 response induces production of the cytokine IL-4, which "suppress[es] Th-1 related phenomena." *See* Exhibit 42 at 4.

[30] Citing Exhibit A-8, S. Otto et al., *General Non-Specific Morbidity is Reduced After Vaccination Within the Third Month of Life—The Greifswald Study*, 42 J. INFEC. 172 (2000).

[31] Exhibit A-11, K. Stratton et al., *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*, Immune Safety Review Committee, Board on Health Promotion and Disease (2002).

[32] This appears consistent with Dr. Gershwin's explanation that "inflammation is basically… infiltrating mononuclear cells," Tr. 21, and "the word 'chronic' implies that [the inflammatory cells] were mononuclear, which is what you'd expect of a virus." Tr. 26.

[33] Citing Exhibit A-2, Kirsten J. Flynn et al. *Virus-Specific $CD8^+$ T Cells in Primary and Secondary Influenza Pneumonia*, 8 IMMUNITY 683 (1998); Exhibit A-10, Kyoko Shinya et al., *Integrated Clinical, Pathologic, Viriologic, and Transcriptomic Analysis of H5N1 Influenza Virus-Induced Viral Pneumonia in the Rhesus Macaque*, 86 JOURNAL

less than 3 days (approximately 63 hours) elapsed between the vaccinations and his death. Thus, the cells must be attributed to a prior infection.[34] However, when I asked Dr. Bassiri specifically whether the mononuclear cells or lymphocytes to which he referred were strictly adaptive immune cells, he admitted: "the truth is there can be a mixed response. So there's probably both innate and adaptive cells that are influxing into that area." Tr. 67.

Dr. Bassiri opined that the infection prompted a Th-1 response. Tr. 51. Namely, naïve T cells differentiated to the Th-1 phenotype. Once differentiated, these cells could not be changed. They would have remained Th-1 after the introduction of the alum.

Dr. Bassiri stated that there is no guarantee that an immune response to a viral infection will be sufficient. Even minor infections can be fatal in rare cases. Factors such as prematurity and infancy can make the immune system more biased to a Th-2 response, which is less effective against infection. Dr. Bassiri stated that as a premature infant, J.H.B. was already less able to fight infection. Indeed, J.H.B.'s infection may have progressed to an asymptomatic pneumonia before he received the vaccinations at issue. Tr. 51. Dr. Bassiri acknowledged that there was no evidence of J.H.B. having pneumonia at that time; however, in his view, the physical examination conducted before administration of the vaccines would not have been a very good way to detect pneumonia. Tr. 77. Dr. Bassiri also stated that the presence of a fever is not necessarily part of the diagnostic criteria for viral pneumonia. Tr. 76. Thus, the fact that J.H.B. was not observed to have a fever at the time of the vaccinations did not rule out the presence of pneumonia.

Dr. Bassiri also opined that J.H.B.'s response to the infection might not have been sufficient, regardless of whether he received vaccinations containing alum. Tr. 57.[35] Dr. Bassiri was asked whether J.H.B.'s behavior after the vaccinations was evidence of an aberrant immune response. He acknowledged that after the vaccinations, J.H.B. was crying inconsolably. Tr. 70. He said this could be evidence of either the incipient infection becoming symptomatic or of a local reaction to the vaccines. Tr. 70-71.

As mentioned earlier, Dr. Bassiri opined that the increased chronic inflammatory cells would have taken 3-5 days to influx. This would conflict with Dr. Gershwin's opinion that if those cells were analyzed, they would have shown the Th-2 phenotype and would be evidence of skewing in that direction.[36] However, Dr. Bassiri acknowledged that this opinion was based upon his

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OF VIROLOGY 6055 (2012); Exhibit A-13, Ellen T.R. Watkiss et al., *Innate and Adaptive Immune Response to Pneumonia Virus of Mice in a Resistant and a Susceptible Mouse Strain*, 5 VIRUSES 295 (2013); Exhibit 44, Kim et al.

[34] This would mean the infection had been present as little as 9 hours or as long as 2 days, 9 hours at the time of vaccination.

[35] Dr. Bassiri acknowledged: "The vast majority of rhinovirus and enteroviruses do NOT induce pneumonia… The vast majority of babies infected with rhinoviruses or enteroviruses develop symptoms… from which they recover. The exceptions to this rule are infants with undiagnosed severe immunodeficiency. If J.H.B. had a severe immunodeficiency, that alone could have caused his death and "then there is no reason to implicate vaccines". Exhibit C at 3. However, Dr. Bassiri did not claim that J.H.B. had an immunodeficiency. Dr. Gershwin said there was no evidence that J.H.B. did. Tr. 43.

[36] Dr. Gershwin opined: "had the pathologist… isolated those cells… they would find that the cells… were those that were more of a Th-2 bias." Tr. 21. Dr. Gershwin also stated that either a Th-1 or Th-2 response would generate inflammation. Tr. 21.

interpretation of medical "jargon" that was in the autopsy report and that the report did not determine the phenotype of these cells. Tr. 91.

iii. Response to Petitioners' Argument about Timing

As stated above, Dr. Bassiri opined that J.H.B.'s rhinovirus or enterovirus was present and was progressing toward pneumonia for some time prior to the receipt of vaccinations. This was based on Dr. Bassiri's interpretation of the language in the autopsy report that "chronic inflammatory cells" means lymphocytes and his opinion that lymphocytes take at least 3-5 days to influx in the lungs. Tr. 83. This argument also relates to the timing of the alleged reaction to the vaccinations.

As stated above, Dr. Gershwin opined that the alum conveyed via vaccines would quickly and temporarily skew the immune system toward a Th-2 response. Dr. Gershwin stated that this would begin "within hours." In support of this proposition, Dr. Gershwin cited the articles by McKee, Kim, and Pourcyrous.

In response, Dr. Bassiri stated that *if* there is found to be a causal link between multiple vaccines containing alum and skewing toward a Th-2 response, he does not know what the medically acceptable time period would be. Tr. 81-82. He did not respond to Dr. Gershwin's discussion of the McKee finding that mice displayed a Th-2 response "within hours" and that Kim's mice would have begun a Th-2 response sooner than when they were measured 3-5 days after vaccination. Dr. Bassiri agreed that Pourcyrous et al. recommended monitoring of premature infants for up to 48 hours after vaccination because of the risk of cardiorespiratory events. Tr. 74. He agreed with counsel that 48 hours was the "critical time period" in which "evidence of distress in the little one is going to show." Tr. 74. He stated that there was a difference between distress and infection. Tr. 75. But Pourcyrous associated "distress" with the release of C-reactive protein. Dr. Bassiri stated that C-reactive protein may be released by the liver in response to any inflammatory response, such as an infection. Tr. 75.

Because the Pourcyrous article was introduced only at the hearing, respondent also addressed it in his post-hearing brief, saying that J.H.B. died approximately 60 hours after vaccination, "well outside" the 48 hours during which Pourcyrous recommends that an infant be monitored. Respondent's Post-Hearing Brief at 9.

III. EVALUATION OF THE EVIDENCE

A. *Althen* Prong One: Can Alum Skew A Premature Infant Toward a Th-2 Immune Response at a Critical Time?

Under *Althen* Prong One, petitioners' burden is to present preponderant evidence of a medical theory causally connecting vaccination and injury. *Althen*, 418 F.3d at 1278. Petitioners are not required to come forward with either medical literature or epidemiological evidence. *Andreu*, 569 F.3d at 1380. Any evaluation of such evidence is completed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id*. For the reasons described below, I find that petitioners have satisfied the first *Althen* prong.

As detailed above, petitioners' expert Dr. Gershwin stated that a premature infant is less able, but still capable, of mounting a Th-1 response to a mild viral infection. Dr. Gershwin theorized that the introduction of alum would divert the infant's ongoing immune response away from the Th-1 response and towards a Th-2 response during a critical window of time. Thus, prematurity, infancy, and alum together cumulatively prevent the infant from responding effectively to the infection. As an expert in clinical immunology and pediatrics, Dr. Gershwin is well-qualified to so opine. Tr. 11-15. I also find that his theory was reasonable and based on the best evidence available.

Respondent's expert Dr. Bassiri accepted certain aspects of Dr. Gershwin's theory and did not adequately refute the others. As an initial matter, Dr. Bassiri agreed that a Th-1 response is the most effective innate response to a viral infection, while Th-2 is more effective against bacteria. Dr. Bassiri also agreed that premature birth and infancy both create a bias toward Th-2. Dr. Bassiri cited Thayyil-Sudhan for the proposition that that these factors weaken, but do not completely eliminate, the premature infant's ability to mount a Th-1 response. Exhibit A at 4 (citing Exhibit 9, Tab C1, Thayyil-Sudhan et al.).

Dr. Gershwin provided a similar summary of the Thayyil-Sudhan article, stating: "BCG vaccine shows no difference in effectiveness *between premature and term infants* using the Th-1 response to the antigen as measured by a tuberculin skin test and lymphocyte migration inhibitory test." Exhibit 9-A at 3 (emphasis added). However, Thayyil-Sudhan actually evaluated the effectiveness of vaccinating *preterm infants* (all born at under 35 weeks of gestation) *at two different times*: (1) shortly after birth at 34-35 weeks post-conception, compared to (2) at 38-40 weeks post-conception. Exhibit 9-C1 at 1. They found that the two groups of preterm infants had "similar uptake and cell-mediated immune responses" when measured 6-8 weeks after vaccination. *Id.* at 2. They concluded: "Prematurity itself seems to be an unlikely cause for poor vaccine uptake and cell-mediated immune response. Thus we conclude that babies born at 34 weeks can be safely vaccinated with BCG within days after birth, which is the time when they are discharged from hospital in developing countries." *Id.* at 3. In other words, Thayyil-Sudhan compares the immune responses of two groups of pre-term infants at different ages. Thayyil-Sudhan does not compare pre-term infants to full-term infants. It is also important to note that Thayyil-Sudhan measured the immune responses that had developed 6-8 weeks after vaccination, which is well outside the time period at issue in this case.

I also note that Thayyil-Sudhan concluded that both groups – the infants vaccinated shortly after pre-term birth, and the infants vaccinated several weeks after pre-term birth – could build an immune response. However, Thayyil-Sudhan did not evaluate whether the infants could effectively respond to a coincident viral infection while also receiving vaccinations.

Thus, Thayyil-Sudhan does not refute Dr. Gershwin's theory. First, Thayyil-Sudhan's study was designed to evaluate the effectiveness of vaccinating premature infants immediately after birth compared to several weeks later when they reached full post-conception age (38-40 weeks). Exhibit 9, Tab C1 at 1. Thayyil-Sudhan did not find any differences between the two groups. *Id.* Second, Thayyil-Sudhan measured the infants' immune responses 6-8 weeks after vaccination. *Id.* Therefore, this study has limited relevance to Dr. Gershwin's theory, which addresses the immune responses to infection and vaccinations in the short-term, i.e., in a critical window of time shorter than one week. I accept Thayyil-Sudhan et al. for the proposition that premature infants, either immediately after birth or several weeks later, are able to mount an immune response to the vaccine

antigen within 6-8 weeks. However, the study does not rebut Dr. Gershwin's theory that premature infants are somewhat biased toward a Th-2 response and does not address vaccine skewing toward a Th-2 response or an infant's vulnerability to a coincident infection. Dr. Gershwin also stressed that infancy, prematurity, and alum would each weaken the Th-1 response and have a *cumulative* effect.

The experts' most critical area of disagreement was as to how the immune system would respond to a viral infection *followed by* vaccinations containing alum. The experts agreed that upon encountering a viral infection, an infant's immune system would direct naïve T cells toward a Th-1 response. Dr. Gershwin opined that alum in vaccines would skew an infant's immune system toward a Th-2 response. Dr. Bassiri questioned the amount of alum that would have this effect, but accepted the proposition.

Dr. Gershwin also said that even if the viral infection and the Th-1 response were present first, the immune system is producing new naïve T cells all the time. Alum would prevent new naïve T cells from joining the ongoing Th-1 response. Instead, the new naïve T cells would skew toward a Th-2 response. Consequently, the Th-1 response would not be as robust as it would have been absent the alum. Dr. Gershwin opined that this could allow the viral infection to progress to a fatal outcome, and it likely did so in this case. Tr. 28-30.

Dr. Bassiri agreed that a viral infection would cause naïve T cells to differentiate to a Th-1 phenotype, while vaccines would cause them to skew toward a Th-2 type. But Dr. Bassiri argued that once T cells are differentiated, it is very difficult to change them (either *in vivo* or *in vitro*). (But as noted above, Dr. Gershwin did not argue that differentiated cells would be changed.) Dr. Bassiri opined: "[I]t's the initial skewing that's the most important. What develops after that is in the local environment." Tr. 59. He acknowledged that the immune system continues to build its response to the infection and that millions of naïve T cells are produced each day. Tr. 58. Dr. Bassiri did not specifically address where those new naïve T cells would be directed, although his theory of terminal differentiation would imply that whatever exposure occurred first (viral or vaccine) would be critical and the response triggered by the first exposure would continue. I asked Dr. Bassiri the following question: if the immune system first encounters a viral infection and begins a Th-1 response, then encounters 5 vaccines (which for the purposes of the question, skew toward a Th-2 response), do the vaccines "reduce the effectiveness of the [ongoing Th-1] response because… the new cells that are being produced to come to the battle basically are skewing Th-2 and not Th-1?" Tr. 59-60. Dr. Bassiri responded: "I don't know of any direct answer to that, at least from looking at the literature." Tr. 60.

The experts agreed that a premature infant is already susceptible to viral infection because his immune system is already biased toward a Th-2 response. It also appears clear that the production of a Th-2 response to alum would weaken a further Th-1 response, allowing the viral infection to progress. Dr. Gershwin's explanation that the ongoing production of Th cells would skew to the Th-2 side upon vaccination seemed reasonable and persuasive. Dr. Gershwin further argued that it was unlikely that J.H.B. had an ongoing pneumonia at the time that he was vaccinated because he had no symptoms whatsoever and the pediatrician's physical exam found no problems. These facts increase the likelihood that J.H.B.'s infection did not progress to pneumonia until after the vaccinations skewed his immune system away from the effective response.

Dr. Gershwin and Dr. Bassiri agreed that alum will predispose the immune system toward a Th-2 response. Exhibit A at 4; Tr. 56. They then spent significant time arguing about what amount of alum would have that effect on a human infant. Dr. Gershwin provided studies by McKee and Kim for the proposition that alum can skew mice's immune responses toward Th-2. Dr. Gershwin stated that multiple vaccines would convey a "comparable" amount of alum to an infant and would have a similar effect. In response, Dr. Bassiri contended that the results of the McKee and Kim studies were dose-dependent and the dose given to an infant was not comparable.

After full consideration, I find that the available studies provide some support for Dr. Gershwin's theory, that *some* amount of alum can produce some skewing toward a Th-2 response in an infant. It is significant that the experts agree that alum can skew toward a Th-2 response. Furthermore, it is difficult to carry out ethical and practical studies of immune responses in humans (particularly infants) *in vivo*. For this reason, special masters and judges often consider studies conducted on animals and extrapolate from them to assess what could happen in humans. I am also inclined to do so in this case and I am not persuaded by Dr. Bassiri's arguments. First, Dr. Bassiri's initial opinion relied on his calculation that McKee's mice received 1,000-times more alum than an infant would. After Dr. Gershwin observed that the Alhydrogel contained only 2% alum, Dr. Bassiri then acknowledged that some of the mice received Alhydrogel, meaning they received only 40-times more alum than the infants receiving alum in vaccinations. Because Dr. Bassiri initially included only the first calculation, his opinion is less persuasive. Also, McKee "did not notice significant differences between the innate response induced by these two formulations" used in the study. Exhibit 42 at 3. This would suggest that alum is less dose-dependent that Dr. Bassiri claimed.

Dr. Bassiri also highlighted Kim's finding that reducing the dose of alum from 20 μg to 5 μg (a 4-fold reduction) resulted in a significant reduction of IL-4 producing Th-2 cells. Tr. 63-64 (citing Exhibit 44 at 9, 11). However, even the 5 μg dose produced *some* Th-2 response.

Finally, Dr. Bassiri did not adequately explain his calculations. He referenced "a typical mouse's body weight" without stating what that would be. Exhibit A at 4. Furthermore, Dr. Gershwin suggested that the calculation based on body weight was too simplistic. Tr. 38-40. Dr. Bassiri did not respond to this critique. For these various reasons, I find that these animal studies may be predictive of how the alum in vaccines would affect an infant, although they are difficult to extrapolate. Neither am I persuaded by Dr. Bassiri's argument that alum would not have a systemic effect throughout an infant's body. The studies have some persuasive value in that they demonstrate Th-2 skewing, even if they are not definitive in demonstrating how much alum would be necessary to systematically alter the immune response in an infant.

Dr. Bassiri's next response to Dr. Gershwin's theory was that if an infant's immune system can be skewed by *any* alum, it would be the alum delivered in small amounts, on a daily basis, through food and household products. Exhibit A at 5. Dr. Bassiri said that an infant ingests approximately 1 liter of formula containing approximately 0.225 mg of aluminum each day. Exhibit A at 5. However, if alum has only a temporary effect and is dose-dependent, it would stand to reason that the 1.2 mg of alum delivered via multiple vaccines, all at once, would have a greater effect than the 0.225 mg of alum ingested in the diet on a given day. But the most important testimony on this issue came from Dr. Gershwin, who with the NIH has done a lot of work on aluminum and immunity. Dr. Gershwin said alum is put in a vaccine to adsorb the antigen, and that spreads it out and increases the efficacy of the vaccine. Eventually the antigen becomes saturated,

meaning that it is fully covered by alum and cannot adsorb any more. Any additional alum does not have any effect. Tr. 35. Therefore, this argument from Dr. Bassiri is not persuasive.

The experts also discussed the significance of the available epidemiological evidence. Dr. Bassiri contended that epidemiology would have detected any causal association between alum and impaired response to commonplace viral infection. He noted that millions of infants receive millions of vaccines each year. In response, Dr. Gershwin stated that epidemiology would not detect the course of events at the center of his theory. Namely, his theory specifically addresses the scenario of a *young* infant, born *prematurely*, who has an *early*, *asymptomatic* infection at the time of vaccination. I am inclined to agree with Dr. Gershwin that epidemiology would be unlikely to detect this rare fact pattern depending on multiple factors. Additionally, petitioners are not required to present epidemiological evidence to satisfy *Althen* Prong One or any other aspect of their case. *See Capizzano*, 440 F.3d at 1326 (concluding that requiring epidemiological studies is contrary to *Althen* and impermissibly raises petitioner's burden); *see also Grant v. Sec'y of Health and Human Servs.*, 956 F.2d 1144, 1148-49 (Fed. Cir. 1992) (finding no error where the special master found preponderant evidence of vaccine causation "in the face of weighty epidemiological evidence" and concluding that the epidemiological studies are "probative medical evidence" but "are not dispositive of the actual causation question").

Additionally, in *Shyface*, the Federal Circuit accepted the petitioners' theory that an infection and the vaccines together caused the death, although neither could be said to be the "predominant" cause. 165 F.3d at 1353. The Federal Circuit held that the vaccines must play a substantial role in the cause of the harm, but need not be the sole or even predominant cause of the harm. In the present case, Dr. Gershwin's theory is entirely consistent with *Shyface*. Dr. Gershwin made clear that the mild virus, prematurity, infancy, and the introduction of alum in the vaccines all converged and that each factor was indispensable to the fatal outcome. His theory depends on the premature infant initially having a mild infection, but that does not become fatal absent the introduction of the alum. Thus, the alum plays a substantial role in causing the injury, even if it is not said to be the sole or even predominant cause of the injury.

In light of all of the above and in consideration of the record as a whole, I find that petitioners have presented a medical theory causally connecting vaccines containing alum with a temporary skewing toward a Th-2 response, which can negatively impact a premature infant's response to an incipient viral infection. Therefore, petitioners have satisfied *Althen* Prong One.

B. *Althen* Prong Two: Did Alum Skew J.H.B. Toward a Th-2 Response at a Critical Time?

Under *Althen* Prong Two, petitioners must demonstrate by preponderant evidence a logical sequence of cause and effect showing that the vaccination was the reason for the injury. *Althen*, 418 F.3d at 1278. Proof of medical certainty is not required. *Bunting*, 931 F.2d at 873. For the reasons described below, I find that petitioners have satisfied *Althen* Prong Two.

The experts stated that J.H.B. acquired an asymptomatic viral infection before or around the time he received the vaccinations. The experts agreed that there were no signs of illness, but disagreed as to the significance of the lack of signs or symptoms at the time he was examined by this pediatrician. Dr. Gershwin suggested that if J.H.B. had an ongoing viral infection without any signs or symptoms, J.H.B.'s immune system must have been keeping the infection at bay. This

would make it difficult to explain why he died. Tr. 29. In contrast, Dr. Bassiri suggested that a viral infection might not be symptomatic at the outset; rather, it takes some time for symptoms to develop.[37] Dr. Bassiri also stated that J.H.B.'s well-child visit would not have been a good way to detect pneumonia. However, it is noted that it appears that the child had a thorough and clear medical examination by his pediatrician on the day that he was vaccinated. Regarding J.H.B.'s lack of symptoms of a rhino- or enterovirus prior to vaccination, each expert's opinion is somewhat speculative. Dr. Gershwin relies on the lack of signs or symptoms before or after the vaccinations and in particular at the time of his physical examination. Dr. Bassiri relied on what he referred to as medical jargon in the autopsy report where it indicated the presence of mononuclear cells in the lung, which to him indicated an infection that had been present for several days prior to the vaccination. However, the experts agreed that the autopsy report did not state whether those cells bore the Th-1 or Th-2 phenotype. Indeed, the testing that would have determined that fact was not performed.

The experts also agreed that because J.H.B. was a premature infant, he was biased toward a Th-2 response that would be less effective at fighting viral infection. They disagreed about how impaired that response would be. Dr. Gershwin opined that solely based on infancy and prematurity. J.H.B. would be impaired but still able to fend off a mild viral infection. He stressed that "most kids, the vast, vast majority, will not die of an entero or rhinoviral pneumonia unless they have some otherwise significant compromise of their immune system." Tr. 20. Dr. Bassiri opined that a premature infant like J.H.B. would be able to mount a Th-1 response to infection. However, the infant's Th-1 response might be "either… sufficient or… insufficient to take care of the infection." Tr. 57. Dr. Bassiri's opinion was based on observations of children with RSV infections. Tr. 57. He stated that some children "receive the best of care" but still die. Tr. 57-58. He further stated: "there is a mortality rate associated with RSV infection, especially in premature infants regardless of whether they've been vaccinated." Tr. 58. Dr. Gershwin countered, however, that RSV is more aggressive than rhino- or enterovirus. Tr. 95. Based on J.H.B.'s course over the last several days of his life and the fact that the autopsy only found a relatively innocuous virus, I find that Dr. Gershwin's explanation is more likely.

The experts agree that J.H.B. had no signs of a viral infection before January 28, 2013, at approximately 3:20 p.m., when he received vaccines containing approximately 1.2 mg of alum. Exhibit 3 at 3-4. After vaccination, he cried inconsolably, which his mother perceived as unusual. He was put to bed after being fed. On August 31, 2013, at 5:30 a.m., he was found cold to the touch. He was pronounced dead at 6:16 a.m., approximately 63 hours after vaccination. Upon autopsy, J.H.B.'s cause of death was categorized as "acute viral pneumonia." A nasopharyngeal swab showed rhino- or enterovirus. His lungs were found to contain "increased chronic inflammatory cells (right greater than left)."

Dr. Gershwin opined that these facts support a logical sequence of cause and effect between the vaccines and J.H.B.'s death. Normally, he would not expect a common rhino- or enterovirus to progress to pneumonia and death, even in a premature infant. Therefore, some "significant compromise of [J.H.B.'s] immune system" must have caused this fatal result. Importantly, neither

[37] Dr. Bassiri's example was that a person infected with influenza ("flu") who is not vaccinated against the flu and doesn't have protection against it may be "carrying and shedding the virus for a minimum of 24 hours prior to showing any signs or symptoms, perhaps up to 2 days." Tr. 55.

Dr. Gershwin nor Dr. Bassiri could identify a factor other than the alum in the vaccinations that could have compromised J.H.B.'s immune system. Dr. Gershwin opined that it was the alum in the vaccines and the experts agreed that alum can skew the immune system toward a Th-2 response. Although there is no direct evidence of the extent to which J.H.B. mounted a Th-1 or a Th-2 response because that test was not done at autopsy, Dr. Gershwin provided a logical explanation of J.H.B.'s course and his unexpected death. Respondent and his expert Dr. Bassiri did not present a persuasive alternative explanation. Thus, petitioners have established that J.H.B.'s vaccines were a but-for cause and a substantial factor, acting in conjunction with his immature immune system and the mild virus, to cause his death. They have also established a logical sequence of cause and effect under *Althen* Prong Two.

C. *Althen* Prong Three: Is There a Medically Acceptable Temporal Relationship between J.H.B.'s Vaccinations and his Death?

Finally, under *Althen* Prong Three, petitioners must show a proximate temporal relationship between vaccination and injury. *Althen*, 418 F.3d at 1278. "[This] prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1353.

As explained above, petitioners' theory is that when a premature infant receives vaccinations containing alum, the immune response directs naive T-cells to a Th-2 response. The naive T cells are prevented from joining the ongoing Th-1 response against a normally innocuous viral infection, which develops into a fatal pneumonia. Petitioners also contend that this happened to J.H.B. Under *Althen* Prong Three, petitioners need to show that that this occurred within a medically acceptable period of time.

Dr. Gershwin contended that the innate immune system reacts "very, very quickly" and that alum would skew the innate immune response "within hours." Tr. 30. Dr. Bassiri noted that in the McKee study, the introduction of alum triggered the production of a Th-2 innate immune response within 4 hours. Exhibit 9 at 3 (citing Exhibit 42 at 3). The McKee study and the opinions of both experts support the proposition that alum would produce some skewing toward a Th-2 response fairly quickly.

This is also supported by Pourcyrous, who observed that within 72 hours of receiving vaccines, a majority of pre-term infants displayed abnormal elevations of C-reactive protein, which might be associated with "immune activation." Exhibit 14 at 1. Pourcyrous also reported that 16% (39/239) of the preterm infants had "cardiorespiratory events." Exhibit 14 at 2. Thirty-seven of the infants experienced those cardiorespiratory events within 48 hours, but the remaining two infants were within 66 hours. Exhibit 14 at 2. Dr. Gershwin stated that Pourcyrous was consistent with his opinion about the timing in this case. Dr. Bassiri emphasized that the majority of the cardiorespiratory events occurred within 48 hours of vaccination and that Pourcyrous recommended monitoring an infant for that period. Tr. 74. In his post-hearing brief, respondent also noted that monitoring was recommended for 48 hours and that J.H.B. died approximately 60 hours after vaccination. Respondent's Post-Hearing Brief at 9. Dr. Bassiri and respondent are correct that Pourcyrous stated that the critical time period for observing pre-term infants was the first 48 hours after vaccination. However, 48 hours is not a bright-line cut-off as to when an adverse event can become evident. Indeed, J.H.B. did become cranky and sleepy after the vaccinations. Tr. 110. It is

not unreasonable that it would take more than 48 hours for the mild virus in J.H.B.'s carriage to evolve into a fatal pneumonia. Also, Pourcyrous found that 2 of the 39 infants' cardiorespiratory events occurred between 48 - 66 hours after vaccinations. This timing is comparable to the timing in J.H.B.'s case.

Thus, Dr. Gershwin opined that administering multiple vaccines containing alum would *quickly* and *temporarily* skew an infant's innate immune system toward a Th-2 response and away from an ongoing Th-1 response to an incipient viral infection, during a critical window of time. As a result, the otherwise innocuous viral infection would evolve to a fatal pneumonia. Dr. Gershwin offered some literature in support for this timing. He also indicated that J.H.B.'s incipient infection progressed and led to death within approximately 63 hours of infection, which is consistent with the timing he presented.

Dr. Bassiri did not contradict the literature presented by Dr. Gershwin. Additionally, Dr. Bassiri did not specifically state whether the temporal relationship between J.H.B.'s vaccinations and his death was medically acceptable. When Dr. Bassiri was questioned on this point, he stated that he didn't know what the appropriate time period would be. Tr. 81-82.

Based on my full consideration of the relevant evidence, I find that petitioners have satisfied *Althen* Prong Three.

IV. CONCLUSION

For the foregoing reasons, I find that petitioners have established entitlement to compensation. They have established and applied a theory quite consistent with *Shyface*, in which vaccines played a substantial role, in conjunction with a mild infection and other factors, in causing J.H.B.'s unfortunate death. A separate damages order will issue.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master